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(71) Applicants *(for all designated States except US)*: MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065 (US). McNEIL-PPC, INC. [US/US]; Van Liew Avenue, Milltown, NJ 08850 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SIMS, Robert, T. [US/US]; 5080 Anderson Road, Holicong, PA 18928 (US). SLIVKA, William [US/US]; 9425 Meadowbrook Lane, Philadelphia, PA 19118 (US).

(74) Common Representative: MERCK & CO., INC.; Patent Dept., 126 East Lincoln Avenue, Rahway, NJ 07065 (US).

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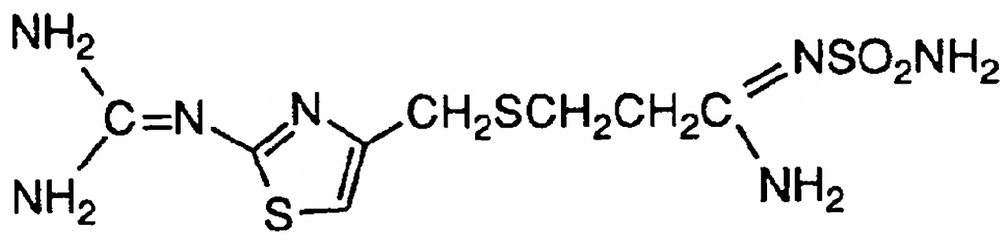
(54) Title: H_2 ANTAGONIST-ALGINATE COMBINATIONS



(I)

(57) Abstract

This invention relates to pharmaceutical compositions for use in the treatment and relief of indigestion, sour stomach, heartburn and other gastrointestinal disorders in mammals, including humans, by administering compositions comprising: (i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of formula (I) and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs and (ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the alginates and optionally (iii) an anti-flatulent amount of simethicone.

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TITLE OF THE INVENTION
H_2 ANTAGONIST-ALGINATE COMBINATIONS

BACKGROUND OF THE INVENTION

H_2 antagonists are commonly prescribed to treat and prevent ulcers in the walls of the stomach, duodenum or esophagus. H_2 antagonists are also used to treat non-ulcerative conditions. Damage to the mucus lining surrounding these tissues enables destructive action of stomach acids which erodes the underlying tissue. Commonly known H_2 antagonists for the treatment of ulcers include cimetidine, ranitidine, nizatidine, roxatidine and famotidine.

Combinations of alginates with certain H_2 antagonists have been disclosed. See U.S. Pat No. 5,007,790 which discloses a solid state drug containing (cimetidine)/polymer (sodium alginate); GB 2222772 which discloses the H_2 antagonist ranitidine and alginic acid. GB 2,207,865 discloses a wound healing agent comprising H_2 antagonist (famotidine) with carrier such as an alginate wherein the composition is used to treat wounds rather than as a gastric acid inhibitor. EP-290,229-B discloses an H_2 antagonist (cimetidine) plus an antacid or alginate. See also U.S. Pat. No. 4,996,222. It is known that with certain H_2 antagonists, an alginate added to treat gastroesophageal reflux can promote oxidation of the H_2 antagonist to a biological inactive form and additional ingredients have to be added to prevent this reaction.

Combinations of antacids and alginates have been used to provide symptomatic relief of gastroesophageal reflux. See *Martindale's Extra Pharmacopoeia* at page 1432. There is a need, however, to employ a drug combination with the advantages of an alginate or alginic acid to prevent gastroesophageal reflux ("GER") in combination with an H_2 antagonist selected from famotidine or its salts, hydrates, steroisomers or polymorphs thereof, to treat and prevent the discomfort associated with indigestion, sour stomach, heartburn or other gastrointestinal disorders including GER. Additional antoxidants may be added to the claimed famotidine/alginate combination to prevent oxidation of famotidine to a less active metabolite. There is a need to employ a combination wherein

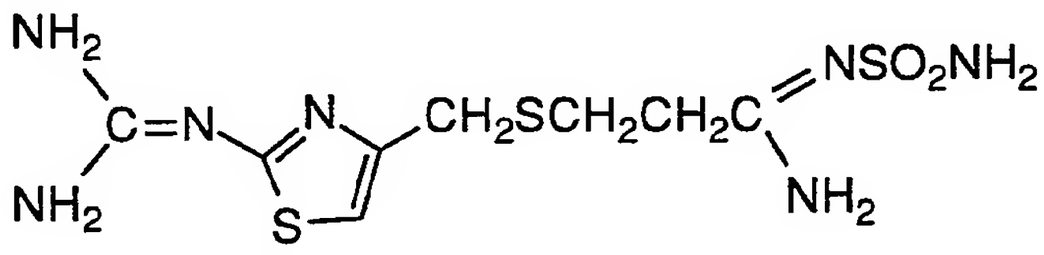
an advantage is that the overall symptoms of gastrointestinal distress can be effectively treated with a combination of the most powerful H_2 antagonist available with an alginate wherein the combination simultaneously relieves and prevents symptoms associated with excess gastric acid secretion or evolution in the stomach and esophagus respectively.

The present invention therefore provides an effective dual and synergistic treatment of gastrointestinal disorders such as GER using the combination of famotidine and its salts, hydrates, or pharmacologically active stereoisomers or polymorphs with an alginate. The claimed combination is particularly useful for treating gastroesophageal reflux disorder at nightime since famotidine or the biologically active forms of famotidine has a long-lasting effect (9 hours) thereby aiding in the prevention of heartburn and other gastrointestinal distress while the alginate aids in eliminating the rafting effect. Other H_2 antagonists that may be employed in this invention include cimeditine, ranitidine, nizatidine, and roxatidine.

DETAILED DESCRIPTION OF THE INVENTION

This invention claims pharmaceutical compositions for use in the treatment of mild stomach and esophagus disorders including the prevention and treatment of heartburn. The composition comprises:

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of the formula:



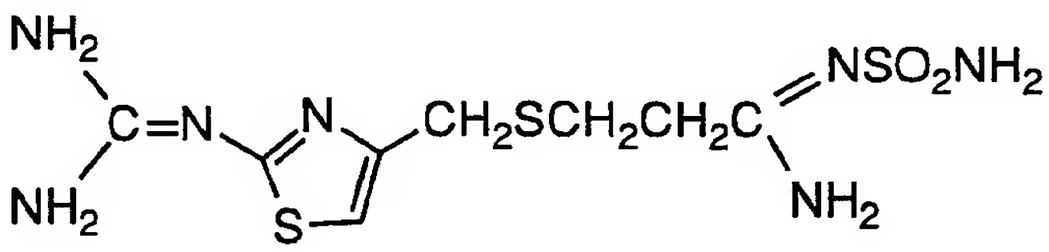
and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of an alginate and optionally

(iii) an anti-flatulent amount of simethicone.

This invention is also directed to a method of preventing and treating indigestion, sour stomach, heartburn, overindulgence, gastro-esophageal reflux and other gastrointestinal disorders in mammals, including humans, in need of treatment thereof, comprising administering to such organism:

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of the formula:



and its pharmaceutically acceptable salts, hydrates, or stereoisomers or polymorphs and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of an alginate and optionally

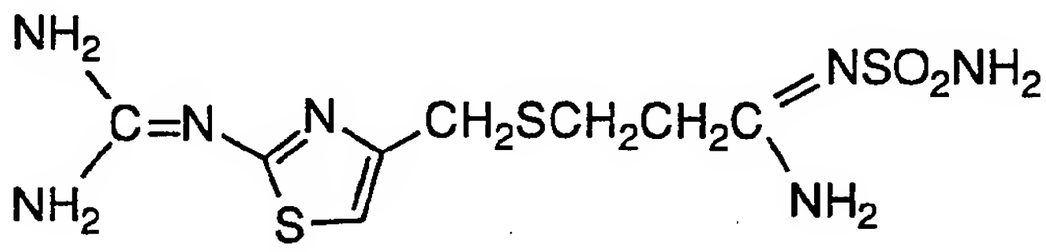
(iii) an anti-flatulent amount of simethicone.

The term mammals or mammalian organism includes but is not limited to man, dog, cat, horse and cow.

The term treatment encompasses the complete range of therapeutically positive effects associated with pharmaceutical medication including reduction of, alleviation of and relief from the symptoms or illness which affect the organism.

Famotidine may be purchased in bulk quantities as it is currently available on the market and formulated via typical formulation processes with alginates selected from alginic acid which is suitable for tablet formulations or sodium alginate which is suitable for liquid formulations of the claimed combination or other pharmaceutically acceptable salts of alginic acid. Famotidine as a prescription drug product is sold under the trademark PEPCID®. Simethicone, an optional anti-flatulent, is also readily available in commercial quantities.

The pharmaceutical compositions of the present invention are useful in the treatment of various mild gastrointestinal disorders including indigestion, sour stomach, overindulgence and heartburn. In particular, an alginate combined with an H_2 antagonist selected from famotidine, a compound of the formula:



or its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs is useful for the prevention and treatment of various gastrointestinal disorders such as indigestion, sour stomach, or heartburn. The utilization of the currently known biologically active forms and/or salts or hydrates of famotidine in combination with an alginate selected from alginic acid or sodium alginate or other pharmaceutically acceptable alginate salt or hydrate is advantageously used to treat mild gastro-intestinal disorders including flatulence if simethicone or another anti-flatulent such as alpha-galactosidase (ADG) is added as an optional ingredient. In particular, the claimed combination is used to treat the symptoms associated with gastric acid secretion while simultaneously treating the symptoms of gastroesophageal reflux. The animal, patient, or organism in need of treatment thereof therefore benefits from the claimed pharmaceutical composition.

H_2 antagonists are well known in the treatment of ulcers and other gastrointestinal disorders and may be used, according to the present

invention, in combination with an alginate and an optional anti-flatulent such as simethicone. H_2 antagonists used for ulcer therapy fall into four major structural classes: imidazole derivatives; substituted furans; aminoalkylphenoxy derivatives and guanidinothiazole compounds. Famotidine (N'-(aminosulfonyl)-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl]methyl]thio]propanimidamide), a member of the latter class, is a competitive inhibitor of histamine H_2 receptors and its primary pharmacological activity is the inhibition of gastric acid secretion. Famotidine suppresses both the acid concentration and the volume of gastric acid secretion. Famotidine is well tolerated and has minimal side effects and thus advantageously may be used in the present invention in combination with an alginate. Famotidine is also the most potent and selective H_2 antagonist. The combination of famotidine or its pharmaceutically effective salts, hydrates, stereoisomers or polymorphs with an alginate provides a combination which simultaneously and selectively provides relief from and prevention of discomfort and injury to the stomach, esophagus, or duodenum from excess production of gastric acid. Furthermore, famotidine in combination with an alginate may not interact with alcohol so that it may be administered prior to or during ingestion of meals or beverages which contain alcohol and, therefore, a patient in need of rapid treatment of gastrointestinal distress may take the drug combination at an appropriate time which may be during a meal in which alcohol was consumed. The combination of an alginate with famotidine provides relief of gastroesophageal reflux while also providing long acting relief from and treatment of gastrointestinal disorders associated with gastric acid secretion.

A therapeutically active stereoisomer or polymorph of famotidine may be employed substantially free of other stereoisomeric forms or polymorphs. Substantially free should be taken to mean at least 90% of one distinct stereoisomer or polymorph.

The combination of famotidine which is a highly potent H_2 antagonist with an alginate reduces the size and weight of all pharmaceutical delivery forms or combination formulations and therefore improves patient compliance or tolerance. The tablet or capsule form of

this combination is more readily swallowable by patients in need of treatment thereof.

Famotidine or its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs is advantageously used in the present invention in combination with alginic acid or sodium alginate. The amount of famotidine used in the present invention in humans may range from 2.5 mg/day to 80 mg/day. Advantageously, 2.5 to 40 mgs/day is administered in combination with 200-500 mgs/day of an alginate. The amount of simethicone added, if employed, may range in humans from 10-1,000 mgs/day. The quantity of simethicone added varies depending upon the desired anti-flatulent strength. It is sold commercially and utilized in various forms and dosages and combinations. Maximum strength simethicone administered alone may be 125 mgs/tablet and taken 4-5 times daily. ADG may be employed as an anti-flatulent in doses of 290 to 31,000 Galactosidase International Units (GaIU), particularly 675 to 2250 GaIU. (WO 90/14101) The quantities of each of the active ingredients may vary depending upon the severity of the condition and the particular biochemistry and need of the patient or other organism in need of treatment thereof. The quantities of the active ingredient may also vary depending upon whether the active ingredients are administered in tablet or liquid form or via some other suitable delivery method. A physician or clinician or veterinarian of ordinary skill in the art may readily determine suitable dosages of any prescription medication containing the claimed invention. The combination claimed in the instant invention is advantageously administered orally.

The present composition may be administered in the form of tablets, lozenges, wafers, caplets, gelcaps, capsules, elixirs, effervescent formulations, chewable tablets, syrups or suspensions or via other known and effective delivery methods. For oral administration, the active ingredients may be admixed with a pharmaceutically acceptable diluent such as lactose, sucrose, cellulose, dicalcium phosphate, calcium sulfate, mannitol, and, in a liquid composition, ethyl alcohol. Acceptable emulsifying or suspending agents such as PVP, gelatin, natural sugars, corn sweeteners, natural and synthetic gums such as acacia, sodium

alginate, guar gum, agar, bentonite, carboxymethylcellulose sodium, polyethylene glycol and waxes, may also be admixed with the active components. Where necessary, lubricants such as magnesium stearic acid talc or magnesium stearate, and disintegrators or superdisintegrators such as starch, sodium starch glycolate or cross-linked PVP may also be included. Electrolytes such as dicalcium phosphate, sodium benzoate, sodium acetate and sodium chloride may also be used. Other inactive ingredients that may be added to the claimed active combination include sodium or potassium bicarbonate, magnesium trisilicate, aluminum trisilicate, aluminum hydroxide gel, lactose, sorbitol, aspartame and sodium saccharide.

The active components may also be formulated in sustained release or effervescent formulations. The sustained release formulations also include layered formulations which provide for distinct release ratio and thus may be more effective in allowing for short and long term relief.

The following examples illustrate the compositions of the present invention which may be readily prepared and as such are not to be considered as limiting the invention set forth in the claims.

EXAMPLE 1

alginate/famotidine Tablet

alginic acid	500 mg
famotidine	40 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 2

alginate/famotidine Tablet

alginic acid	500 mg
famotidine	20 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 3

alginate/famotidine Tablet

alginic acid	500 mg
famotidine	15 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 4

alginate/famotidine Tablet

alginic acid	500 mg
famotidine	10 mg
PVP	15 mg
Avicel PH101	40 mg

Magnesium Stearate	4 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 5

alginate/famotidine Tablet

alginic acid	500 mg
famotidine	5 mg
PVP	15 mg
Avicel PH101	40 mg
Magnesium Stearate	4 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 6

alginate/famotidine Sustained Release

alginic acid	600 mg
famotidine	40 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 7

alginate/famotidine Sustained Release

alginic acid	600 mg
famotidine	20 mg
PVP	30 mg
Avicel PH101	80 mg
Magnesium Stearate	8 mg
Methocel E10MCR	66 mg
Methocel K100MLV	200 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 8

alginate/famotidine Solution

sodium alginate	500 mg
famotidine	10 mg
g.s. syrup	5 ml
sorbitol	680 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

EXAMPLE 9

alginate/famotidine Solution

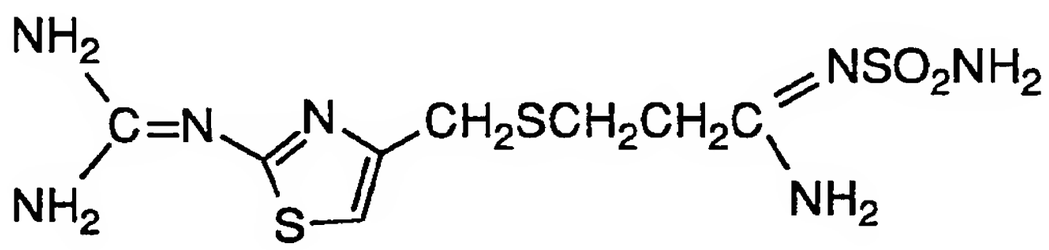
sodium alginate	500 mg
famotidine	20 mg
g.s. syrup	5 ml
sorbitol	680 mg
Magnesium Trisilicate	25 mg
Sodium bicarbonate	170 mg
aluminum hydroxide gel	100 mg

Simethicone may be added to each of the above formulations or examples to provide anti-flatulent relief. The quantity of simethicone administered to a patient in need of treatment thereof is the typical known dosage range to treat flatulence (20-40 mgs per tablet or 5 ml liquid dosage form). The inactive ingredients in the tablet form may further include dextrates, mannitol, magnesium stearate, Yellow 10, collodial silicon dioxide and Blue 1 or Red 27 while the liquid form(s) may further include inactives such as butylparaben, carboxymethylcellulose sodium, flavors, hydroxypropyl methylcellulose, microcrystalline cellulose, propylparaben, and purified water. The previous examples are to be construed as non-limiting and additional dosages and dosage forms or routes of administration may be varied depending upon the individual patient being treated for either the primary (excess acid leading to gastrointestinal or esophageal disturbance or damage) or secondary (infections) symptoms of gastrointestinal disorders. In addition, known pharmaceutically acceptable excipients or agents may be added as inactive ingredients to the claimed active combination in a variety of forms including tablets, capsules, or time-release medicaments.

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for use in the treatment of gastrointestinal disorders such as indigestion, sour stomach, overindulgence and heartburn in a mammals, including humans comprising:

(i) an amount effective in the relief of gastrointestinal or espohagus disorders of an H_2 antagonist selected from a compound of the formula:



and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs and

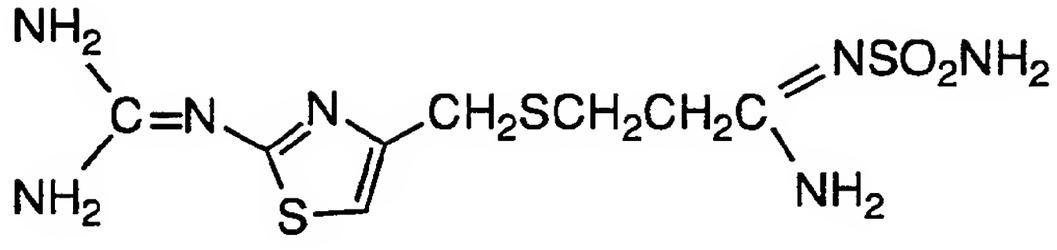
(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the alginates and optionally

(iii) an anti-flatulent amount of simethicone.

2. The composition of Claim 1 comprising between 5 mg to 40 mgs of famotidine and 200-500 mgs of an alginate and optionally 20-40 mgs of simethicone.

3. A method of treating gastrointestinal disorders such as indigestion, sour stomach, overindulgence, gastroesophageal reflux and heartburn in a mammalian organism in need of such treatment, comprising administering to such organism:

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of the formula:



and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the alginates and optionally

(iii) an anti-flatulent amount of simethicone.

4. A method according to Claim 3 wherein the composition administered to a mammalian organism in need thereof comprises:

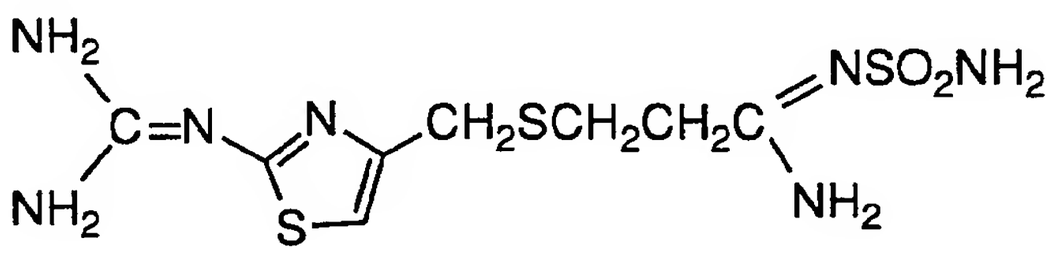
(i) a tablet of 10 mgs of famotidine and

(ii) 500 mgs of alginic acid and optionally

(iii) 20-40 mgs of simethicone.

5. A method of reducing the size and weight of a pharmaceutically effective amount of an alginate/H_2 antagonist combination dosage form which comprises combining

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of the formula:



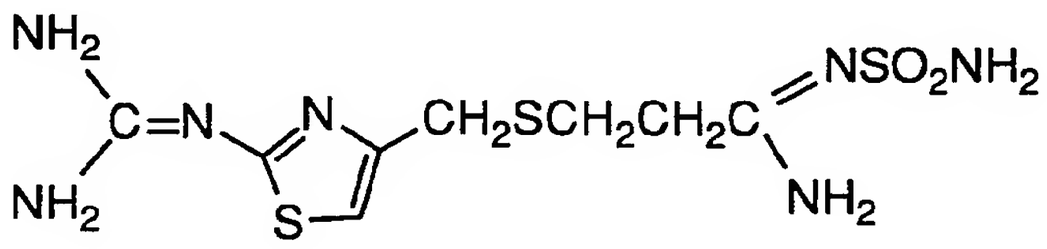
and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the alginates and optionally

(iii) an anti-flatulent amount of simethicone.

6. A method of treating gastrointestinal disorders, overindulgence and pain before or during ingestion of a meal accompanied by alcoholic beverages, comprising:
administration of a combination of

(i) an amount effective in the relief of gastrointestinal or esophagus disorders of an H_2 antagonist selected from a compound of the formula:



and its pharmaceutically acceptable salts, hydrates, stereoisomers or polymorphs wherein the famotidine does not interact with ethanol from the ingestion of the alcoholic beverage and

(ii) an amount effective in relief of gastrointestinal or esophagus disorders of at least one of the alginates and optionally

(iii) an anti-flatulent amount of simethicone.

7. A method of treating gastroesophageal reflux (GER) in patients in need of treatment thereof using a combination of famotidine

or its pharmaecutically acceptable salts, hydrates or isoforms and an alginate selected from alginic acid or sodium alginate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/07521

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 9/14, 9/20, 9/48, 47/00
US CL :424/439, 451, 464, 489

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/439, 451, 464, 489

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG
search terms: famotidine, alginate, simethicone, gastrointest?, gastroesoph?

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,204,118 (GOLDMAN ET AL.) 20 April 1993, see entire document.	1-7
X,P	US, A, 5,229,137 (WOLFE) 20 JULY 1993, see entire document.	1-7
Y,P	US, A, 5,244,670 (UPSON ET AL.) 14 SEPTEMBER 1993, see entire document.	1-7
Y,P	US, A, 5,260,072 (ROCHE ET AL.) 09 NOVEMBER 1993, see entire document.	1-2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search
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Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer
HOWARD C. LEE

Telephone No. (703) 308-0196

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